Reducing Invalid Connections with Microstructure-Driven Tractography

Gabriel Girard[1,2,3], Alessandro Daducci[1,3], Laurent Petit[4], Jean-Philippe Thiran[3], Kevin Whittingstall[5,6], Rachid Deriche[2], Demian Wassermann[2,†], Maxime Descoteaux[1,6,†]

1 Sherbrooke Connectivity Imaging Lab, Computer Science Department, Université de Sherbrooke, Canada **2** Project Team Athena, INRIA Sophia Antipolis – Méditerranée, France **3** Signal Processing Lab (LTS5), École Polytechnique Fédérale de Lausanne, Switzerland **4** Groupe d'Imagie Neurofonctionnelle, Institut des Maladies Neurodégénératives - UMR 5293, CNRS, CEA University of Bordeaux, France **5** Department of Diagnostic Radiology, Université de Sherbrooke, Canada **6** Sherbrooke Molecular Imaging Center, Department of Nuclear Medicine and Radiobiology, Université de Sherbrooke, Canada † These authors contributed equally.

INTRODUCTION: Diffusion-weighted imaging (DWI) tractography has become the tool of choice to probe the human brain's white matter (WM) *in vivo*. However, tractography algorithms produce a large number erroneous/invalid streamlines [1] largely due to complex ambiguous local fiber configurations (e.g. crossing, kissing or fanning). Moreover, the relationship between the resulting streamlines and the underlying WM microstructure characteristics, such as axon diameter, remains poorly understood [2]. The distinctive aspect of our tractography algorithm from previous methods is the active use of microstructure information about fascicles during the tracking. This enables us to solve areas of complex tissue configuration and separate parallel fascicles with different microstructure characteristics, hence improving the overall tractography process.

METHODS: We used the deterministic tractography *AxTract* [5] to simultaneously trace fascicles and estimate their axon diameter characteristics. The main hypothesis driving *AxTract* is that the mean diameter of the axons composing a fascicle varies slowly along its pathway [6]. *AxTract* locally selects the peak of the fiber Orientation Distribution Function (ODF) that better follows the microstructural information estimated in previous propagation directions. The microstructural information is estimated using the *ActiveAx* model [3] generalized to multiple fiber populations per voxel [7], implemented in the efficient *AMICO* framework [4]. AxTract estimates, in each fiber ODF peaks, the mean diameter associated to signal fitted cylinder response functions: the axon diameter index [3,4,7]. The axon diameter index is then used to select the propagation direction. *AxTract* streamlines are compared to the same deterministic tractography algorithm without using the axon diameter index information, referred as conventional deterministic tractography (CDT). The only difference between *AxTract* and CDT is thus the selection of the propagation direction at tracking positions with multiple direction: CDT always selects the propagation direction that minimize the curvature of the streamline, *AxTract* selects the propagation direction with axon diameter index the closest to the axon diameter index associated to the streamline [5].

DATASET: We used *Phantomas* to generate a kissing configuration between two fascicles and obtained the fascicle directions at each voxel. For each fascicle direction, the DWIs were independently simulated for a distribution of parallel cylinders diameter, with a fixed distinct mean diameter per fascicle [7]. The synthetic DWIs were generated with the *in vivo* imaging protocol (details below) using *Camino*, and then contaminated with Rician noise at signal to noise ratio (SNR) 20. To evaluate reconstructed streamlines, we used the *Tractometer* [1] connectivity analysis. We report the Valid (VC) and Invalid Connections (IC) for both *AxTract* and CDT (VC: % of streamlines connecting expected regions of interest , IC: % of streamlines connecting unexpected regions of interest).

We tested our method on the MGH adult diffusion dataset (34 subjects) [8] (552 volumes, b-values up to 10,000s/mm^2, δ=12.9ms, Δ=21.8ms, 1.5mm isotropic voxels). We used the provided pre-processed DWIs corrected for motion and EDDY currents. Fiber ODFs were computed from spherical deconvolution [9] using *Dipy* on a single b-value shell of 3000s/mm^2. T1-weighted 1mm isotropic resolution images were registered to the diffusion images using *ANTs*. The brain parcellation was then obtained using *FreeSurfer* and WM fascicles were obtained using *TractQuerier*. We report the changes in streamline count as: $(\text{count}_{\text{AxTract}} - \text{count}_{\text{CDT}})/ \text{count}_{\text{CDT}}$. T1-weighted images were also registered to the *ICBM 2009a Nonlinear Symmetric Atlas* [10] for voxel-based group analysis.

RESULTS AND DISCUSSION: Figure 1 (top row) shows the ground truth directions used to generate the synthetic data and the peaks extracted from the fiber ODFs scaled by the axon diameter index estimated with *AMICO*. Figure 1 (middle and bottom rows) show the streamlines reconstructed using *AxTract*. VC increases from 52.5% with CDT to 87.2% with *AxTract* and the IC decreases from 42.6% to 8.5% respectively. This shows that *AxTract* can distinguishes fascicles in complex architectures when these have different axon diameters. *AxTract* privileges following the direction which minimises the deviation from axon diameter index of the fascicle being traced while the CDT approach is to minimise the directional deviation. In doing so, *AxTract* is able to better resolve the kissing scenario and decreases the percentage of IC.

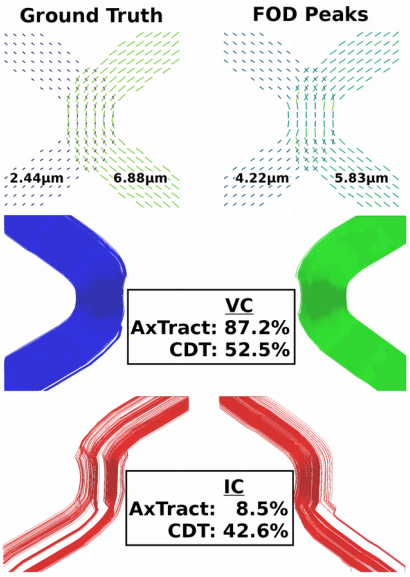

Figure 1: Tractometer evaluation of AxTract and CDT on a synthetic kissing dataset (SNR=20).

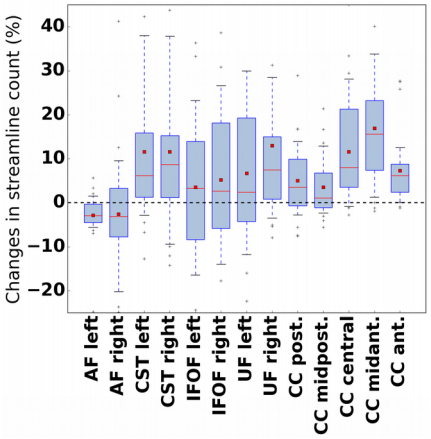

Figure 2: Changes (%) in streamline count between AxTract and CDT accross fascicles of 34 subjects. The red square indicates the mean, the red line indicates the median, the box extends from 1st to 3rd quartile and the wiskers from the 5th to 95th percentile.

The changes in streamline count between *AxTract* and CDT across five fascicles of 34 healthy subjects are shown in Figure 2. It shows that using the same tractography parameters, only changing the selection of the propagation direction with *AxTract*, the mean relative changes in streamline count across the 34 subjects increases for most of the selected fascicles, e.g. the CST (left: 11.6%, right:11.6%) and the UF (left: 6.7%, right: 13.0%). This suggests that *AxTract* has a consistent effect on some of the reported fascicles reconstruction across subjects and possibly overall increasing VC. Further research is needed to validate these changes in the streamlines distribution *in vivo*. Figure 3 shows the average occurrence map of *AxTract* selecting a different propagation direction than CDT over the 34 subjects. *AxTract* changed the propagation direction in 38% of tracking steps where multiple directions were available. Figure 3 suggests this happen more frequently in crossing areas underneath to the cerebral cortex.

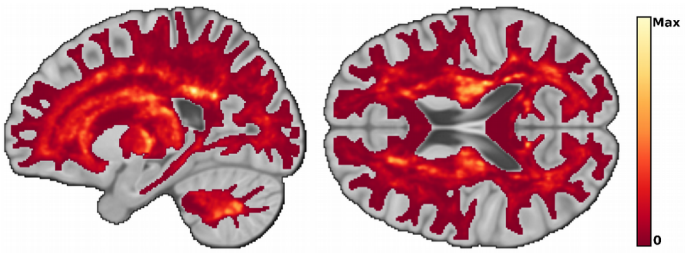

Figure 3: Average occurrence map of AxTract selecting a different propagation direction than CDT over the 34 subjects.

AxTract enables the possibility of solving the tracking through complex WM areas using axon diameters information and reducing invalid connections.

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